Remarks / Arguments

As a result of this amendment, claims 1 and 3-16 are pending in the application. Claim 2 has been cancelled. Claims 1 and 3-9 have been amended. New claims 10-16 have been added. No new matter has been added.

Rejection under §112, first paragraph

In the official action, claims 1 and 3-8 were rejected under 35 U.S.C. §112, first paragraph, as lacking an adequate written description.

In his argument, the examiner states that the specification fails to disclose structural limitations of PDE 2 inhibitors, and only discloses the functional limitations "compounds that inhibit PDE 2" and "compounds with IC_{50} less than 10μM". This is incorrect, and also overlooks the fact that the claims refer to "selective" PDE 2 inhibitors. Example one, 6-(3,4-dimethoxybenzyl)-1-[1-(1-hydroxyethyl)-4-phenylbutyl]-3-methyl-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one, on page 9 lines16-17, is identified and tested and shown to inhibit human and bovine PDE 2 more strongly than PDE 1, PDE 3B, PDE 4B, PDE 5, and PDE 7B. Of these, the greatest degree of selectivity is shown relative to PDEs 3B, 4B, and 7B. The applicants have also provided the generic structural formula (I) and its definition on page 4 to illustrate certain selective PDE inhibitors, though they do not maintain that it covers all such materials.

In his argument, the examiner further states that it is obvious from the term "PDE 2 inhibitor", these compounds will inhibit PDE 2 selectively. This is incorrect. A compound may be a PDE 2 inhibitor and also inhibit other PDEs significantly, in which case it would not be called a selective PDE 2 inhibitor relative to those other PDEs. In the present application, the term "selective PDE 2 inhibitor" is defined as a compound which inhibits human PDE 2 under the test conditions indicated in the specification more strongly than the human cAMP PDEs 3B, 4B, and 7B.

The examiner maintains that the specification fails to provide any structural information or characteristics, other than the compounds of formula (I), for the skilled artisan to ascertain what compounds may be useful for the instant invention. He further states that the applicants

have not specifically defined any of the PDE 2 inhibitors that fall within the broad genus claimed (and states that the claims read on all PDE 2 inhibitors). As pointed out above, this is incorrect. Applicants are claiming the use of selective PDE 2 inhibitors, not all PDE 2 inhibitors, and have provided an example of such a material. The examiner further states that the applicants do not describe any structural characteristics commonly possessed by all PDE 2 inhibitors such that one of skill in the art would recognize that the applicants were in possession of the full breadth of the claimed invention. Again, the examiner misses the point that applicants are claiming the use of selective PDE 2 inhibitors, not all PDE 2 inhibitors.

The present applicants have discovered that selective PDE 2 inhibitors have utility in the treatment of disorders of perception, concentration, learning, and/or memory; they have exemplified one such material and have provided the general formula of a subclass of such materials, and have provided test procedures by which those skilled in the art can determine whether other PDE 2 inhibitors are selective for PDE 2 relative to PDE 3B, 4B, and 7B. Applicants maintain that their invention is the use of selective PDE 2 inhibitors in treatment of certain disorders, and believe that those skilled in the art would understand this upon reading the specification.

Rejection under §112, second paragraph

In the official action, the examiner rejected claims 1 and 3-9 under §112, second paragraph, on grounds that the claims are indefinite, the examiner maintaining that the language "improved perception" in claim 1 renders the claims indefinite in terms of how the improvement of perception is to be achieved. He also refers to the Merriam-Webster's Collegiate Dictionary for two definitions of the term "perception", which he maintains support his contention that "one of ordinary skill in the art would not recognize a way to improve perception since perception could depend on the experience one has."

The examiner has overlooked definition No. 4 in the cited dictionary definition, namely, "a quick, acute, and intuitive cognition". This is the definition which is most apt in the present context, which deals with mental issues. There is nothing indefinite about the word "perception" as used in the present claims. Secondly, regarding the examiner's concern over the concept of

"improving" perception, concentration, learning and/or memory, the applicants have amended the claims to recite "A method for treating a disorder of.....", and removed the word "improving". Treatment of disorders was clearly contemplated in original claim 2.

Claims 3-8 were rejected on grounds that the language "disorder of perception..... memory" lacked antecedent basis. The present amendment to claim 1 obviates this rejection.

Claims 3-8 were rejected on the ground that "disorder of perception" is indefinite for the same reason "perception" was considered indefinite. This issue has been discussed above. The term "perception" is not indefinite.

Claims 3-8 were rejected for indefiniteness, the examiner maintaining that the claims are indefinite as to what disorders are encompassed by the claim language. Applicants maintain that those skilled in the art would understand what is meant by "disorder ..... is a result of" dementia, stroke, craniocerebral trauma, Alzheimer's disease, Parkinson's disease, or depression. Whether the disorder is a direct result or an indirect result of the listed conditions should not be an issue, nor should the degree of association between the disorder and the underlying condition. Claim language can be no more precise than the technology it relates to, and here we are dealing with medical conditions. Medical science is not always exact. Diagnoses are not always correct. Medical research is ongoing. The claim language is deemed to be sufficiently definite.

Rejection under §102(b)

Claims 1 and 3-8 were rejected under §102(b) as anticipated by Rupp (U.S. patent 5,141,936). The examiner maintains that Rupp teaches a method of administering an amount of trequinsin, also known as HL-725, a potent inhibitor of isolated PDE II, to rabbits, and concludes that the presently claimed therapeutic effect will inherently be present in the method of Rupp, et al.

This rejection is not well-founded. There is no disclosure in the cited reference that the rabbits had any disorder of perception, concentration, learning and/or memory, and also no disclosure of whether the compound administered is a selective PDE 2 inhibitor as required by the present claims. For inherency, it must be certain that the "inherent" aspect asserted by an

examiner is necessarily present in the thing or process disclosed by the reference. This is not the case here.

Rejection under §103

Claims 1, 4, and 9 were rejected under §102(a) as obvious over Haning, et al., (WO 98/40384 and U.S 6,147,884). The examiner maintains that the reference teaches a method of treating cerebrovascular diseases (e.g., stroke) comprising administering to a patient a presently claimed PDE II inhibitory compound of formula (I). He states that the reference does not particularly teach the particular manifestations/symptoms of a stroke (e.g., impaired memory, perception, learning ability), but maintains it would have been obvious to employ the method of Haning in treating disorders of perception, learning, concentration, or memory, because these conditions are known to result from a stroke, and treating stroke would be expected to effectively treat the symptomatic/secondary disorders, absent evidence to the contrary.

Haning discloses medicaments for treatment of cardiovascular and cerebrovascular diseases, diseases of the peripheral blood vessels and diseases of the urogenital tract. See the abstract. The reference states that the compounds "inhibit either one or more of the c-GMP-metabolizing phosphodiesterases (PDE I, PDE II and PDE V)", which "leads to a differentiated increase in c-GMP", which in turn "can lead to an antithrombotic, vasodilatory and/or antiarrhythmic action." See column 13, lines 53-57. At column 13, line 64 through column 14, line 11, the reference states, "They can therefore be used in medicaments for treating cardiovascular diseases such as, for example, for treating hypertension, nueuronal hypertension, stable and unstable angina, diseases of the peripheral and cardial blood vessels, of arrythmias, for treating thromboembolic diseases and ischaemias such as myocardial infarction, stroke, transistory and ischaemic attacks, angina pectoris, peripheral circulation disorders, prevention of restenoses after thrombolytic therapy, percutaneous transluminal angioplasty (PTA), percutaneous transluminal coronary angioplasties (PTCA) and bypass. The relaxing effect on the smooth muscles makes them suitable for the treatment of diseases of the urogenital system such as prostatic hypertrophy, impotence and incontinence. Moreover, they can also be of importance for cerebral vascular diseases."

The reference also discloses test results for the ability of 5 exemplary compounds to inhibit phosphodiesterases (PDE I, PDE II, and PDE V) in vitro. See column 14, lines 52-62.

Haning does not mention treating disorders of perception, concentration, learning and/or memory, although it does mention stroke as the examiner recognizes. However, as shown above, the reference mentions "stroke" only as one of a large number of cardiovascular diseases for which the compounds of the reference can be used. Furthermore, there is no suggestion in the reference that any of the compounds there disclosed is a selective PDE 2 inhibitor, or that a selective PDE 2 inhibitor should be used for treating any of the conditions listed in the reference. Accordingly, it would appear that the examiner's rejection for obviousness in view of this reference constitutes hindsight reconstruction in light of the applicant's disclosure and claims, which is not a proper basis for an obviousness rejection.

Claims 1 and 3-8 were also rejected as obvious over Whalin in view of Egawa. The examiner states that Whalin teaches HL-725 (trequinsin, a potent inhibitor of isolated PDE II activity in vitro) can cause 1) increased basal cAMP accumulation, 2) potentiation of adenosine-stimulated cAMP accumulation, and 3) retardation of the rate of cAMP decay. He cites Egawa for its disclosure that administration of rolipram (a PDE 4 inhibitor) ameliorated certain deficits of learning and memory in rats, and its suggestion that "the ameliorating effects of rolipram might result from the indirect potentiation of various transmitters including cholinergic and noradrenergic systems by an increase in cAMP with the inhibition of PDE 4." The examiner appears to conclude that it would have been obvious ..... to employ trequinsin in a method of treating disorders of memory and learning impairment, because he assumes that the Egawa reference teaches that the amelioration of memory/learning impairment found in Egawa's experiments resulted from an increase in cAMP, coupled with the teaching of Whalin that trequinsin caused increased basal cAMP accumulation.

The Egawa reference states that "These results suggest that the ameliorating effects of rolipram might result from ..... an increase in cAMP with the inhibition of PDE 4." It does not state that it is proven that the amelioration of the deficits of learning and memory are due to an increase in cAMP as implied by the examiner. However, even assuming that this is true, the

combination of the teachings of the Whalin and Egawa references does not make the present claims obvious because there is no suggestion in the references that trequinsin is a selective PDE 2 inhibitor.

New claim 10 is a combination of claims 1 and 9. New claims 11-16 parallel claims 3-8.

Regarding the Haning '884 reference, it is noted that exemplary compounds 18, 39, 40, 49, and 85 fall within formula (I) of the present claims, but none of these compounds appear to have been tested for PDE inhibitory activity, so there is no indication in the reference that compounds of formula (I) of the present claims are PDE 2 inhibitors, and no indication that they are selective PDE 2 inhibitors.

It is also noted that neither trequinsin (HL-725) nor rolopram fall within formula (I) of the present claims.

In view of the above amendments and arguments, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,

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